Long-term outcome of inflammatory bowel disease patients with deep remission after discontinuation of TNF-blocking agents

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2017

Molander , P , Farkkila , M , Kemppainen , H , Blomster , T , Jussila , A , Mustonen , H & Sipponen , T 2017 , ' Long-term outcome of inflammatory bowel disease patients with deep remission after discontinuation of TNF-blocking agents ' , Scandinavian Journal of Gastroenterology , vol. 52 , no. 3 , pp. 284-290 . https://doi.org/10.1080/00365521.2016.1250942

http://hdl.handle.net/10138/311875
https://doi.org/10.1080/00365521.2016.1250942

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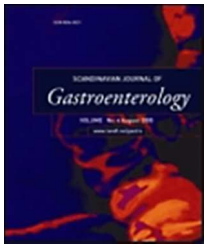

LONG-TERM OUTCOME OF INFLAMMATORY BOWEL DISEASE PATIENTS WITH DEEP REMISSION AFTER DISCONTINUATION OF TNFα–BLOCKING AGENTS

Journal:	*Scandinavian Journal of Gastroenterology*
Manuscript ID	Draft
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Molander, Pauliina; Helsinki University Central Hospital and University of Helsinki, Peijas Hospital, Department of Gastroenterology Färkkilä, Martti; Helsinki University Central Hospital and University of Helsinki, Department of Gastroenterology Kemppainen, Helena; Turku University Central Hospital, Department of Gastroenterology Blomster, Timo; Oulu University Central Hospital, Department of Gastroenterology Jussila, Airi; Tampereen yliopistollinen sairaala, Department of Gastroenterology and Alimentary Tract Surgery Mustonen, Harri; Helsinki University Central Hospital and University of Helsinki, Department of Surgery Sipponen, Taina; Helsinki University Central Hospital and University of Helsinki, Department of Gastroenterology
Keyword:	Crohn's disease, Ulcerative colitis, Relapse, Withdrawal, TNFα-antagonist, Infliximab, Adalimumab

LONG-TERM OUTCOME OF INFLAMMATORY BOWEL DISEASE PATIENTS WITH DEEP REMISSION AFTER DISCONTINUATION OF TNFα–BLOCKING AGENTS

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Key words:

Crohn's disease; ulcerative colitis; relapse; stopping; TNFα-antagonist; infliximab; adalimumab

ABSTRACT:

Background:

Little data exist on the long-term prognosis of patients with inflammatory bowel disease (IBD) after stopping TNFα- blocking therapy in deep remission. Existing data indicate that approximately 50% of patients on combination therapy who discontinued TNFα- blockers are still in remission 24 months later. The aims of this follow-up analysis was to evaluate the long-term remission rate after cessation of TNFα-blocking therapy, the predicting factors of a relapse and the response to restarting TNFα blockers.

Methods:

The first follow-up data of 51 IBD patients (17 Crohn's disease [CD], 30 ulcerative colitis [UC] and 4 inflammatory bowel disease type unclassified [IBDU]) in deep remission at the time of cessation of TNFα-blocking therapy have been published earlier. The long-term data was collected retrospectively after the first follow-up year to evaluate the remission rate and risk factors for the relapse after a median of 36 months.

Results:

After the first relapse-free year, 14 out of the remaining 34 IBD patients relapsed (41%; 5/12 [42%] CD and 9/22 [41%] UC/IBDU). Univariate analysis indicated no associations with any

predictive factors. Re-treatment was effective in 90% (26/29) of patients.

Conclusion:

Of IBD patients in deep remission at the time of cessation of TNFα-blocking therapy, up to 60% experience a clinical or endoscopic relapse after a median follow-up time of 36 months (95% CI 31-41 months). No individual risk factors predicting relapse could be identified. However, the initial response to a restart of TNFα-blockers seems to be effective and well tolerated.

INTRODUCTION

The chronic nature of inflammatory bowel disease (IBD) and lack of recommendations for cessation of TNFα-blocking therapy may lead to long-term maintenance therapy with TNFα blockers as early treatment recommendations have become more widely accepted. With patients achieving remission, the potential severe side effects (i.e. infections, acute infusion reactions, delayed hypersensitivity reactions, risk of neoplasia, and safety issues during pregnancy) and economic issues prompt the questions on cessation of TNFα-blocking therapy.[1,2,3,4] In addition, it is nowise certain that the benefits of TNFα-blocking agents are permanent in the long run.

Several studies show that the overall risk of relapse after discontinuation of TNFα-blocking agents is 44% for Crohn's disease (CD, follow-up range of 6-125 months) and 38% for ulcerative colitis (UC, follow-up range of 6-24 months).[5,6,7,8,9,10,11,12,13,14,15] The relapse risk seems to be lower in IBD patients who are in deep remission (clinical, biological and endoscopic remission) at the time of cessation of TNFα-blocking therapy

compared to those in clinical remission only.[9] Available data are insufficient for giving strong recommendations on at what point safely cease TNFα-blocking therapy. Therefore the decisions should be based on assessment of the patient's individual risks and benefits. In CD several factors have been investigated to identify patients who are more likely to achieve long-term remission after discontinuation of TNFα-blocking agents. The factors that have been associated with a higher risk of relapse are younger age, smoking, longer disease duration, fistulising phenotype, perianal disease, short duration of remission, previous surgical operation, endoscopically active disease, ileocolonic disease at diagnosis and previous TNFα-blocking therapy, high markers of inflammation and high infliximab trough level. On the other hand, mucosal healing, colonic CD, a shorter interval between disease diagnosis and starting anti-TNF, concomitant immunosupressive therapy and absence of antibodies to TNFα-blocking agents seem to decrease the risk of relapse after discontinuation of TNFα-blocking agents.[6,7,10,12,13, 14,15,16] A study by Waught and co-workers shows that 35% of the CD patients with a follow-up for nearly seven years after discontinuation of therapy remained in sustained clinical remission. No specific factor was associated with the duration of CD remission.[17] In patients receiving TNFα-blocking agents for the prevention of post-operative CD recurrence, the risk of relapse after discontinuation is very high (>75%) and the ceasing decision should be based on very good reasons.[18] Importantly, restarting of TNFα-blocking therapy for those who relapsed after stopping treatment seems to be effective and well-tolerated.[5,6,9,10,12]

We have earlier published a prospectively collected 12-month data of cessation of TNFα-blocking therapy in IBD-patients with deep remission.[9] The aim of this study was to evaluate the long-term relapse rate after the first year of follow-up and the predictive

factors for relapse in this study population, as well as the response rate to TNFα-blocking agents after the restart of medication in the case of relapse.

MATERIALS AND METHODS

Patients and study design

All 51 IBD patients in this follow-up analysis were primarily recruited in a prospective multicenter study which was carried out at nine gastroenterological centers in Finland during the period from February 2010 to June 2013.[9] At the time of inclusion all patients were in deep remission (i.e. clinical, endoscopic and faecal calprotectin -based [FC <100μg/g] remission). After the primary study, one UC patient was dropped from the follow-up due to no available data on a patients' report. Clinical notes of all enrolled patients were retrospectively reviewed for this long-term follow-up. All patients had an established IBD diagnosis, had received TNFα-blocking maintenance therapy for a minimum of one year (the median duration of infliximab [IFX] therapy was 13 [n = 46, range 11-77] months and adalimumab [ADA] therapy 27 [n = 5, range 16-36] months), had been in corticosteroid-free remission over a 6-months period prior to the inclusion, were in clinical, FC-based (FC <100 μg/g) and endoscopic remission at the time of inclusion. Due to its small size, the subgroup IBDU of four patients was combined with the UC group.

Given the retrospective design of this study, clinical disease activity was assessed by the physicians' global assessment (asymptomatic patients vs. symptomatic patients indicating active IBD) in patients relapsing after the first year of follow-up and 12 months after the restart of TNFα-blocking therapy. At relapse endoscopic findings were scored, as in our earlier study [9], according to the SES-CD[19] in CD and endoscopic Mayo score in UC and

IBDU.[20] An SES-CD of 3-6 was defined as mildly active disease, 7-15 as moderately active disease, and ≥ 16 as severely active disease.[21] Endoscopic Mayo subscore of ≥ 2 defined active disease.[22]

In a case of a clinical and/or endoscopic relapse after the first year of follow-up, TNFα-blocking therapy was restarted at the same dose and frequency as prior to withdrawal in exception of two patients, whose relapses were treated with oral corticosteroids or mesalazine. Ileocolonoscopy was performed 12 months after the restart of TNFα-blocking therapy in exception of four patients with normal fecal calprotectin levels. Endoscopic activity was defined as mild, moderate, or severe by an experienced gastroenterologist.

Fecal calprotectin assays

FC was measured using the quantitative enzyme immunoassay (the CALPRO® Calprotectin ELISA Test [ALP; Calpro AS, Lysaker, Norway]). The values quoted as normal were < 100 µg/g.[23]

Statistics

The Statistical Package for the Social Sciences (SPSS version 23) for Windows software (SPSS, Chicago, IL, USA) was used for data analyses. Fisher's exact test was used to determine differences in binary variables. The significance was set at $p < 0.05$ and two-tailed tests were used. Kaplan-Meier survival analysis was employed in estimation of relapse-free survival rates, and the log-rank test was used to determine the differences between the groups. The Cox regression of proportional hazards was used to calculate univariate hazard ratios for categorical and continuous variables. The results were given as percentages, as median and range, or as mean and standard deviation (SD).

Ethical statement

The study protocol and all documents of the prior prospective multicenter study were approved by the ethics committee at Helsinki University Hospital and at each participating university central hospital. Because this follow-up study was a retrospective reviewing of patients' medical records, no separate application for ethics committee was needed.

RESULTS

The baseline characteristics are described in Table 1. As established in earlier publication, during the first 12-month follow-up, up to 33% of patients (5/17 [29%] CD and 12/34 [35%]) UC/IBDU) in deep remission relapsed.[10] After the first relapse-free year, 14 of the remaining 34 IBD patients relapsed (40%; 5/12 [42%] CD and 9/22 [41%] UC/IBDU) during median follow-up period of 36 months (1-69; in CD 38 months [3-68] and in UC 35 months [1-69]). Of the14 relapsed patients, endoscopic data were available on 13 at the time of a relapse. Out of five relapsed CD patients, one experienced a severe clinical relapse without endoscopic documentation, two experienced both clinical and endoscopic relapse (SES-CD 8 and10) and two experienced moderate endoscopic relapse without clinical symptoms mean (SES-CD 7 and 9). All UC patients experienced both clinical and endoscopic relapse (mean endoscopic Mayo score 2 [2-3]).

The time-to-relapse curves of all patients are shown in Figure 1. No significant difference was found in the relapse rate between CD and UC/IBDU, p = 0.919.

The risk factors for relapse

Based on univariate analysis (Cox model) risk factors such as diagnosis, gender, disease duration, localization, behavior, smoking, family history, previous surgery, the TNFα-blocking agents used, concomitant medications or duration of the used TNFα-blocking agents were not associated with the risk of relapse, Table 2.

Restarting TNFα-blocking therapy

The response after restarting TNFα-blocking therapy was evaluated in all 29 of 51 IBD patients, Figure 2. The median time of follow-up after retreatment with TNFα-blocking agents was 12 (range 3-19) months. One relapsed UC patient was treated with corticosteroid and another with mesalazine instead of TNFα-blocking agents. After the restarting TNFα-blocking therapy, all except one UC patient achieved clinical remission or response at three months. During the follow-up period, three patients were operated on: one UC patient underwent colectomy less than two months after the restart of TNFα-blocking therapy due to nonresponse and another UC patient underwent colectomy after one year of TNFα-blocking therapy due to loss of response. Furthermore, one CD patient underwent ileo-ceacal resection after one year of TNFα-blocking therapy due to a symptomatic stricture. After a restart of IFX, two UC patients experienced an infusion reaction (one during the second IFX infusion without anti-drug antibody measurement and the other one six months after restarting developing anti-drug antibodies) and were treated with another TNFα-blocking agent. In addition, despite a combination therapy with thiopurins, three patients (one CD and two UC patient) developed low concentrations of anti-drug antibodies, but achieved a clinical response by dose escalation (one CD and one UC patient) or by switching to another TNFα-blocking agent (one UC patient). Twelve months after the restart of TNFα-blocking therapy 20 patients (39%; 8 CD, 12 UC) were still in clinical remission. Six patients with CD and 11 patients with UC underwent a 12-

month follow-up ileocolonoscopy, showing either endoscopic remission (4 CD, 9 UC) or mild activity (3 CD, 2 UC). The remaining three patients (2 CD, 1 UC) had normal calprotectin levels serving as surrogate markers to endoscopic remission.

DISCUSSION

It is well known that TNFα-blocking therapy is effective in inducing and maintaining remission in IBD patients with moderate to severe CD and UC and therefore, for responders the long-term maintenance therapy is recommended.[24,25] However, life-long TNFα-blocking therapy in IBD patients in clinical remission or in deep remission is still questioned, since early treatment with an immunomodulator and/or TNFα-blocking agonist are nowadays recommended [26] and long-term safety issues are still debated.

According to this follow-up study almost 60% of patients relapsed after a median follow-up time of 36 months. No statistically significant difference in the relapse rates between CD and UC was found. Several studies, mainly with CD patients, have been published on the duration of remission after a discontinuation of TNFα-blocking therapy, and only few of these studies have assessed endoscopic activity during a long-term follow-up. It is interesting to note, that across all studies reporting on anti-TNF withdrawal of adult IBD patients in clinical remission, despite heterogeneous study designs and patient populations, the one and two -year relapse rates were reasonably consistent ranging from 21-39% and from 37%-56% respectively.[6,7,8,9,10,11,12,13] These findings are in line with our results despite the fact that no baseline endoscopic remission was required in the majority of those earlier studies. However, recently published long-term data of the patients included in the STORI trial seem to indicate poorer remission rates after cessation

of IFX for sustained remission: the vast majority of CD patients (85%) had to restart the treatment over the course of time.[27] The longest follow-up periods reported are 10 years in CD[14] and 7 years in UC.[15] Cumulative relapse rates in all studies rise over time.

Cessation of TNFα -blocking therapy may be considered for patients with a low relapse risk. The relapse risk may be minimized using predictors that identify those at a clinically meaningful risk of relapse. Achieving deep remission is currently considered to be the most important protective factor in disease relapse after TNFα -blocking therapy withdrawal.[28] Many of the risk factors shown in previous studies have been associated with incomplete remission with ongoing inflammatory disease activity at the time of discontinuation. It seems likely that not only the disease activity at the time of cessation of TNFα -blocking therapy but also previous disease history may have an impact on the risk of disease relapse following TNFα -blocking therapy withdrawal. Factors affecting the duration of a clinical remission after discontinuing anti-TNF therapy remain questionable even today. Moreover, it is very likely that patients' initial response to TNFα -blocking therapy and tendency to maintain sustained remission after therapy withdrawal is based on a patient-unique genetic type of IBD disease.[29,30] Future studies are needed to analyze the correlation of patients' genotype and the duration of remission after discontinued TNFα -blocking therapy. As clear and widely accepted recommendations for discontinuing TNFα -blocking therapy are lacking, it has been stated that biological therapy should not be stopped in patients who have undergone multiple previous operations, demonstrated intolerance to conventional drugs or in whom the disease is difficult to control.[31] A multidisciplinary European expert panel (European Panel on the Appropriateness of Crohn's Disease Treatment II, EPACT-II) considered discontinuing TNFα-blocking therapy to be appropriate after four years, but also after two years if the

patient was in deep remission.[32] The results of our previous study suggested that withdrawal of TNFα-blocking therapy after one year could be possible in IBD patients with deep remission as the duration of TNFα-blocking therapy did not influence the relapse risk over time.[9] Nevertheless, considering the possible adverse events after stopping TNFα-blocking therapy, withdrawal should be considered carefully and discussed with the patient.

After a drug-holiday, the risk of immunization resulting in infusion reactions and loss of response should be considered.[33,34] Unfortunately, most of the studies report only short-term outcomes and therefore more evidence is needed to demonstrate the real efficacy and safety of re-treatment. The studies including longer follow-up periods have reported remission rates from 80 to 92%.[7,8] These findings are in line with our study, all but one of the patients achieved clinical remission or response at three months and the remission rate at one year was considerably high (97%). However, the risk of developing anti-drug antibodies may lead to infusion reaction and loss of response followed by severe problems. In our study, three patients underwent surgery due to no response to re-treatment and five patients developed either anti-drug antibodies and/or experienced an infusion reaction. Taking this into account, withdrawal of TNFα-blocking therapy needs to be considered carefully.

Our study has some limitations.The patient group is limited and heterogeneous and the number of patients in the subgroups low. Moreover, cut-off levels used for endoscopic remission (SES-CD score and endoscopic Mayo score) may have allowed mild endoscopic activity at baseline and also during the follow-up. However, we consider that low baseline FC value as another criterion of remission ruled out patients with notable

inflammatory activity.[35] Furthermore, clinical and endoscopic data after one year of stopping TNFα-blocking therapy was not collected for the study purpose. Therefore clinical scores were not available for all patients at the time of relapse and clinical and endoscopic scores were not available after the restart of TNFα-blocking therapy for all patients. However, the strength of this study is a long term surveillance after cessation of TNFα-blocking therapy in a clinical setting and endoscopic verification of a relapse.

The long-term follow-up demonstrates a fairly high relapse rate after cessation of TNFα-blocking therapy among IBD patients in deep remission. However, two out of five patients seem to remain in sustained clinical remission after cessation of TNFα-blocking therapy, but selecting these patients among potential relapsers is challenging. In relapsers, the response to a restart of TNFα antagonists seems to be effective and fairly well tolerated, even if the formation of anti-drug antibodies may result in to dose escalation or a change of TNFα-blocking agent. Therefore withdrawal of TNFα-blocking therapy should be considered carefully on individual bases.

DISCLOSURES

Statement of authorship: study design (PM, MF, TS), data collection (PM, HK, TB, AJ), statistical analysis (PM, HM), drafting the manuscript (PM, TS), final reading and approval of the manuscript (all authors).

PM received lecture fees from Abbvie, Ferring and MSD and consulting fees from Abbvie, MSD and Takeda. MF received consulting fees from MSD, Abbvie, Janssen, Orion Pharma, Medivir and Roche, and lecture fees from MSD, Abbvie, Bayer, Janssen and

Tillots Pharma. TB received lecture fees from Abbvie and Tillotts Pharma and consulting fees from Abbvie. AJ received lecture fees from Abbvie, Ferring, MSD, Takeda and Tillotts Pharma and consulting fees from Abbvie, Hospira, MSD, Takeda and Tillotts Pharma. TS received lecture fees from Abbvie, AstraZeneca, Ferring, Medac, MSD, Pfizer, Tillots Pharma and Vifor Pharma and consulting fees from Hospira, Takeda, MSD and Tillotts Pharma. HK and HM declare no conflicts of interest.

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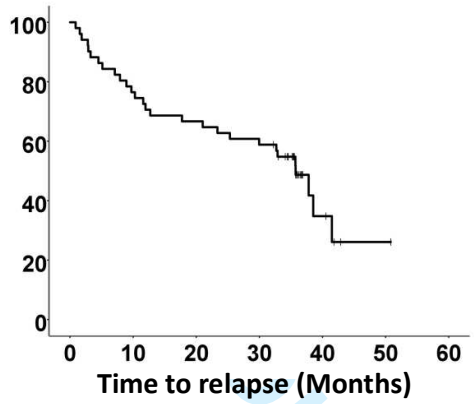
A.



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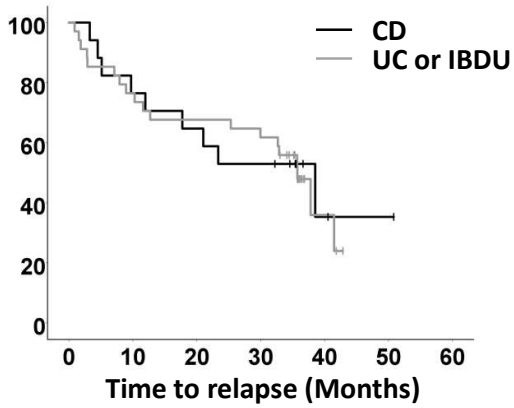

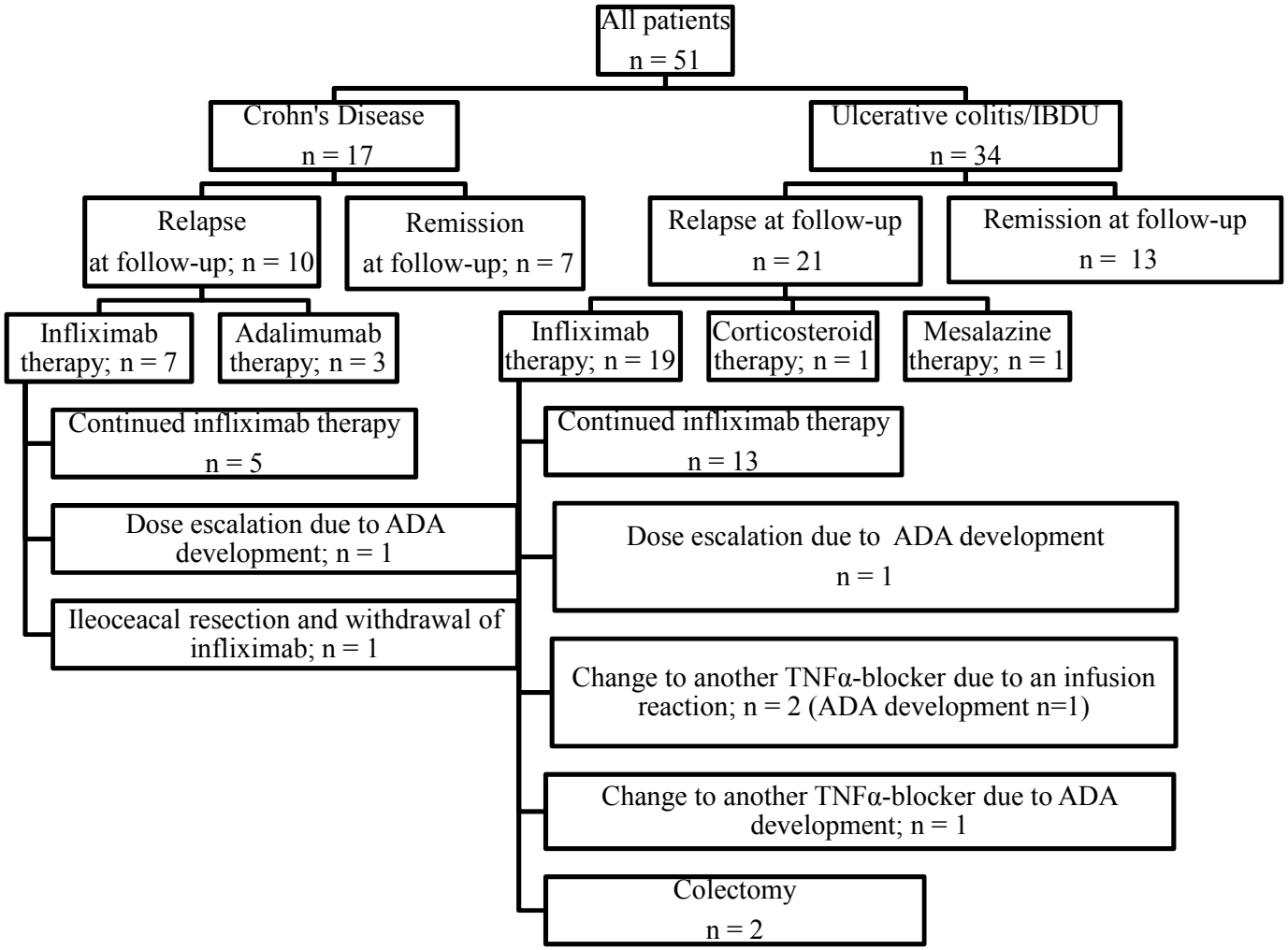

ADA; anti-drug antibody

Table 1. Patients' clinical and demographic characteristics at baseline.

	Ulcerative colitis/ Inflammatory bowel disease unclassified n= 34	**Crohn's disease n= 17**
Male/Female	19/15	8/9
Age at onset (median, range)	26 (8-45)	23 (13-42)
Age at induction (median, range)	32 (13-58)	33 (15-52)
Active smoker, n (%)	4 (12)	4 (24)
Disease duration (median, range)	6 (1-35)	10 (3-26)
Previous bowel surgery, n (%)		8 (47)
Disease behavior (Mb Crohn), n (%) **Inflammatory (B1)** **Stricturing (B2)** **Penetrating (B3)** **B1 ± perianal disease** **B2 ± perianal disease** **B3 ± perianal disease**		 11 (65) 4 (24) 1 (6) 0 1 (6) 0
Disease location	Proctitis 0 Left colon 14 Extensive colitis 20	Ileum (L1) 1 Colon (L2) 4 Ileocolon (L3) 12
Concomitant medications, n (%) **No concomitant medications** **Mesalazine** **Azathioprine/6-MP** **Azathioprine/6-MP+ mesalazine** **Methotrexate + mesalazine**	 1 (3) 4 (12) 12 (35) 17 (50)	 1 (6) 3 (18) 7 (41) 5 (29) 1 (6)
Duration of TNFα-blocking therapy prior to cessation of therapy (months) **Infliximab (median, range)** **Adalimumab (median, range)**	 14 (11-78)	 32 (11-72) 26 (16-36)
TNFα-blocking therapy, n (%) **Infliximab** **Adalimumab**	 34 (100)	 12 (71) 5 (29)

6-MP = 6-Mercaptopurine

Table 2. Predictors for disease relapse in the study population.

Variable	P- value	Hazard Ratio	95% CI lower	upper
Diagnosis; CD versus UC/IBDU	0.919	1.042	0.469	2.316
Male sex	0.780	0.899	0.425	1.899
Age at diagnosis	0.341	0.977	0.931	1.025
Age at diagnosis; <25 y versus ≥25 y	0.073	0.492	0.227	0.069
Age at diagnosis; < 20 y versus ≥ 20 y	0.090	0.508	0.232	1.112
Localisation of CU	0.280	1.704	0.648	4.483
Localisation of CD	0.345	1.000		
L3 versus L1	0.243	3.888	0.398	38.017
L3 versus L2	0.464	0.453	0.054	3.778
Disease behavior (CD)	0.995	1.000		
B1 versus B2	0.793	0.802	0.154	4.177
B1 versus B3	0.995	1.008	0.107	9.470
B1 versus B2 + perianal disease	0.242	2.391	0.555	10.298
Smoking	0.252	1.000		
No versus <10 cigarretts / day	0.125	0.383	0.112	1.306
No versus smoker	0.356	0.644	0.253	1.640
No versus smoker or previous smoker	0.117	0.524	0.233	1.177
Age at induction	0.375	0.981	0.941	1.023
Age at induction; < 30 versus ≥ 30 - 40	0.361	0.662	0.273	1.605
Age at induction; < 30 versus ≥ 41	0.927	0.956	0.362	2.526
Duration of the disease at induction	0.974	1.001	0.949	1.055
Duration of the disease; > 5 - 10 years	0.173	1.876	0.760	4.630
Duration of the disease; ≥ 11 years	0.447	1.451	0.556	3.784
Previous surgery	0.577	0.739	0.255	2.140
Positive family history	0.791	0.876	0.331	2.324
TNF α-blocking therapy used; IFX vs. ADA	0.573	1.418	0.421	4.782
Duration of the TNFα-blocking therapy; median	0.995	1.000	0.977	1.024
CRP at discontinuation; median	0.450	0.935	0.785	1.113
Hemoglobin at discontinuation; median	0.434	1.010	0.985	1.036

CD = Crohn's Disease; UC = Ulcerative Colitis; IBDU = Inflammatory Bowel Disease type Unclassified; TNF = Tumour Necrosis Factor; IFX = Infliximab; ADA = Adalimumab; CRP = C-reactive protein